Methods for Production of the Oxidized Glutathione Composite ...

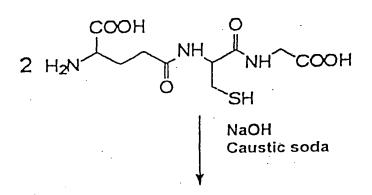
1/26nid A. Kozhemyakin et al.

Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

Fig. 1

2/27 Leonid A. Kozhemyakin et al.

Serial No.: Not Yet Assigned Docket No.: P0633.70014US01



Reduced glutathione

Sodium salt of the reduced glutathione

1) [Pt(NH₃)Cl₂]

Disodium salt of the oxidized glutathione Composite with the cisdiamminedichloroplatinum

Fig 2.

Methods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al.
Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

Methods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al. 4/27
Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

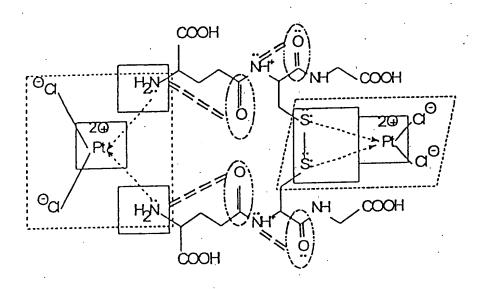


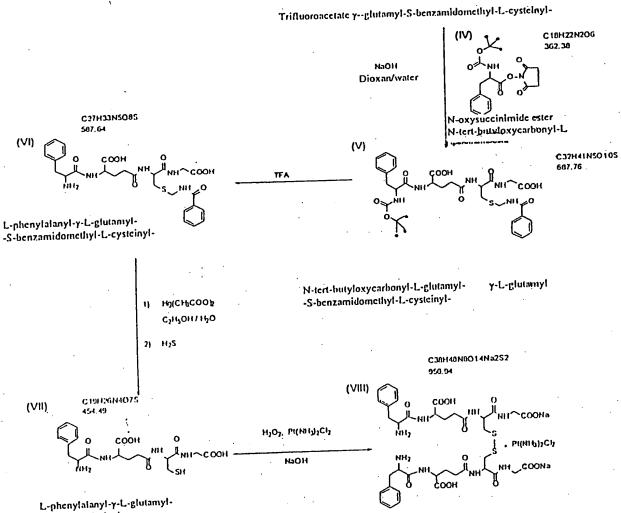
Fig. 5.

Methods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al.
Serial No. Not Yet Assigned

Serial No.: Not Yet Assigned Docket No.: P0633.70014US01

Methods for Production of the Oxidized Glutathione Composite ... Leonid A. Kozhemyakin et al. 6/27

Serial No.: Not Yet Assigned Docket No.: P0633.70014US01



Composite bis-(L-phenylalanyl-y-L-glutamyl)--L-cystinyl-bis-glycine with cis-diamminedichloroplatinum

-L-cystcinyl-glycine

Methods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al.

7/27

Serial No.: Not Yet Assigned Docket No.: P0633.70014US01

COOH

$$H_2N$$
 (s)
 H_2N
 (s)
 $(s$

Fig. 9

$$H_2N$$
 H_2N
 H_2N
 H_2N
 H_3N
 H_4N
 H_4N
 H_5N
 H_5N
 H_5N
 H_5N
 H_6N
 H_6N

Fig. 10.

Methods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al. 8/27
Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

0 сн₃соон

Methods for Production of the Oxidized

Glutathione Composite ...

Leonid A. Kozhemyakin et al. 9/27

Serial No.: Not Yet Assigned Docket No.: P0633.70014US01

Fig. 12.

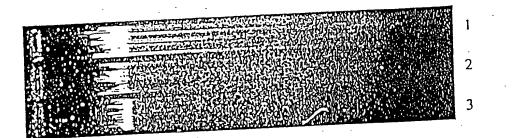


Fig. 13.



Fig. 14.

BEST AVAILABLE COPY

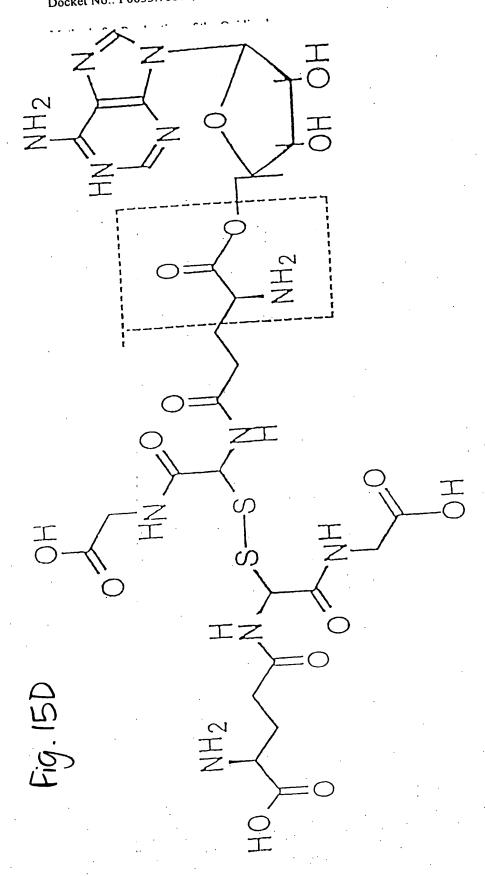
Methods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al. 10/27
Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

Methods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al. 11/27
Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

Methods for Production of the Oxidized

Glutathione Composite ...
Leonid A. Kozhemyakin et al. 12/27
Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

Glutathione Composite ... Leonid A. Kozhemyakin et al. Serial No.: Not Yet Assigned 13/27 Docket No.: P0633.70014US01



Methods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al. 14/27
Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

HO S =0 S

Methods for Production of the Oxidized

Glutathione Composite ...

Leonid A. Kozhemyakin et al. 15/27

Serial No.: Not Yet Assigned

$$\begin{array}{c|c} & & & & \\ & &$$

Fig. 16A

Fig. 16B

Glutathione Composite ...
Leonid A. Kozhemyakin et al.
Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

Fig. 16D

Fig. 16E

Methods for Production of the Children

Glutathione Composite ...

Leonid A. Kozhemyakin et al. 17/27 Serial No.: Not Yet Assigned Docket No.: P0633.70014US01

$$\begin{array}{c|c}
O & CO_2II & H & O \\
N & N & CO_2II \\
N & N & CO_2II \\
N & N & CO_2II \\
N & CO_2II \\
\end{array}$$

Fig. 17A

Glutathione Composite ... Leonid A. Kozhemyakin et al. 18/27 Serial No.: Not Yet Assigned

Docket No.: P0633.70014US01

fig. 17E

Methods for Production of the Oxidized

Glutathione Composite ...

Leonid A. Kozhemyakin et al. 19/27

Serial No.: Not Yet Assigned Docket No.: P0633.70014US01

Machada for Duadwation of the Outdied

Fig. 18B $CO_{2}H$ $H_{2}N$ H_{3} $CO_{2}H$ H_{3} $CO_{2}H$ H_{4} $CO_{2}H$ H_{5} $CO_{2}H$ H_{1} $CO_{2}H$

Methods for Production of the Oxidized

Glutathione Composite ...

Leonid A. Kozhemyakin et al. 20/27

Serial No.: Not Yet Assigned Docket No.: P0633.70014US01

ÇO₂H н H SH H₂N Н H .CO₂H 11_2N Fig. 20A 1:1 ĊO₂H CO₂H Н 1:1 SH

iviethous for Production of the Oxidized

Glutathione Composite ...

Leonid A. Kozhemyakin et al. 21/27

Serial No.: Not Yet Assigned Docket No.: P0633.70014US01

Metnods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al.
Serial No.: Not Yet Assigned
Docket No.: P0633.70014US01

BEST AVAILABLE COPY

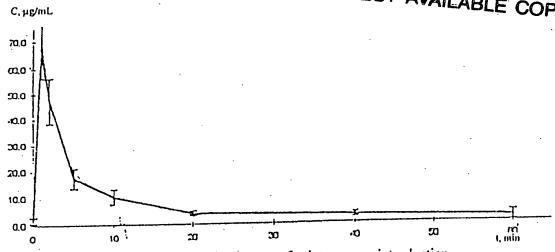
F16.22

Methods for Production of the Oxidized Glutathione Composite ... 23/27

Leonid A. Kozhemyakin et al. Serial No.: Not Yet Assigned Docket No.: P0633.70014US01

The Property of the Control of the C



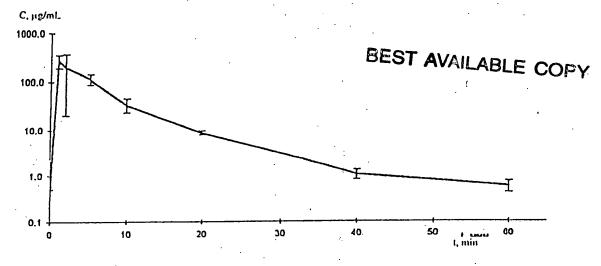


GSSG pharmacokinetic curve for intravenous introduction.

F16.23

Methods for Production of the Oxidized Glutathione Composite ...
Leonid A. Kozhemyakin et al.
Serial No.: Not Yet Assigned

Serial No.: Not Yet Assigned Docket No.: P0633.70014US01



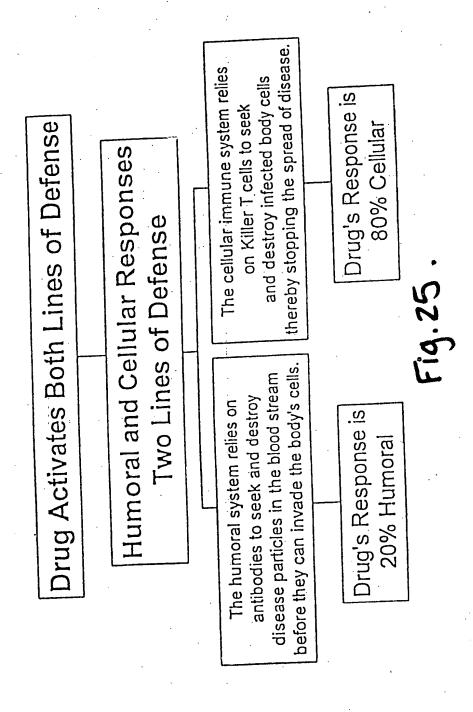
GSSG•Pt pharmacokinetic curve for intravenous introduction

F16. 24

Methods for Production of the Oxidized Glutathione Composite ... 25/27

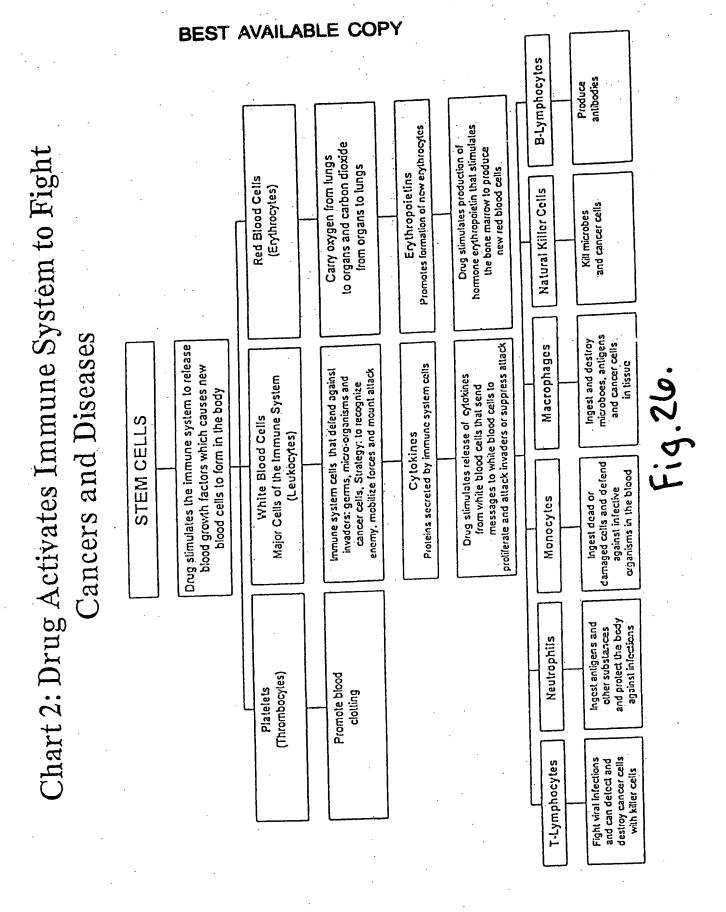
Leonid A. Kozhemyakin et al. Serial No.: Not Yet Assigned Docket No.: P0633.70014US01





Glutathione Composite ...

Leonid A. Kozhemyakin et al. 26/27 Serial No.: Not Yet Assigned Docket No.: P0633.70014US01



Serial No.: Not Yet Assigned Docket No.: P0633.70014US01 numbers of neutrophils
due to
chemotherapy. BEST AVAILABLE COPY stimulates the production of neutrophils and is given to patients who have low GM-CSF with TNF-alpha hemorrhage, soften and turn black. Macrophages begin when they are recruited to the scene destroys cancer
cells, but does not
hurt healthy cells.
Tumors injected to pump-out huge amounts of TNF of Injury or infection. TNF-alpha In 1996, Blogen received FDA approval to market AVONEX for multiple sclerosis. warts, Kaposi's sarcoma, hairy ceil le utemia and malignant melanoma. Chart 3: Cytokines Stimulated by Drug alpha and gamma activates cells effective in treating several forms of hepatitis, genital Interferon is secreted by

B cells and macrophages

and acts in synergy
with IL-2 to activate cytotoxic T cells.
Natural Killer cells
and Thi cells are also proliferate by IL-12 Interleukin-12 stimulated to (11-12) Fig. 27. Cytokines Stimulated by Drug downregulates MHC II
expression on antigen
presenting ocils.
It therects with II-4 to decrease macro-phage inflammatory activity. tole and acts on macrophages to inhibit sytokine production to downreguize suppresses cytokine production from T cells and macriphages. It exerts complex THI type of Thelper cells. It is released by TH2 helper cells and also regulatory offices on CD4+T cells, Natural Killer cells, vascular endobellal ce ils and
B tymphocytes.
Il-10 plays an
Important inhibitory Interleukin-10 (L-16) Intection. Nautrophils are the first line of defense against invading backeria adhers to vascular endothetal cells. This helps neutrophils marginate and enter endothelial cells secrete IL-8 in order to attract ne utrophils and allow them to and are found in all areas of infection. the tissue where they are needed, especially during inflammation and is a powerful chemotactic factor for neutrophils. Macrophages and Interleukin-8 (1.8) number of undescribed ways in inflammatory regulation. by IL-f., it also strongly stimulates hepatocytes to make acute phase proteins In response to inclammation. This cytokine is always found in increased kevels in sites of inflammation and is likely very important in a stem cells are helped differentiation into plasma cells and it is secreted by monocytes, macrophages and bore marrow cells. It acts on proliferating B cells to promote stimulates amibody secretion. Myeloid to differentiate Interleukin-6 (11.6) regulatory manner to decrease the activity of activated macrophages. is released by
Theiper cells of the THZ
subtype and is
particularly active and other allergy-related antibodies. IL-4 acts with IL-10 in an immuno-A B cell stimulated with IL-4 alone on resting and active B cells. On resting B cells and on macrophages becomes a plasma cell secreting IgE IL-4 Increases MMC E differentiation is stimulated and an antibody class switch is induced. expression. On activated B celts, proliferation and Interleukin-4 (F-4) hym phocyta activated killer cells which are re-injected into the body, then killer cells will attack the caroer and destory it. or kidney cancer have been retrieved from the body and exposed in the lab cells would neelve IL. Is chemical message to expand. For example, by cancer ardgens so only those lymphocytes that recognize cancer T-tymphocytes exposed to malignand metanoma and stimulates fymphocytes that have already be en activated to Il-2 to create is produced by lymphocytes. It is a T-cell growth factor Interleukin-2 (F-2) immune responses usually associated with non-specific of infaction and inflammation, and faver, is produced by monocytes, macrophages, and dendritie cells. immure response Interleukin-1 it activates fymphocytes and thereby regulates <u>=</u>

Methods for Production of the Oxidized

Leonid A. Kozhemyakin et al. 27/27

Glutathione Composite ...